REMARKS

Claims 1-9 were pending in the instant application. By this amendment, Applicants have amended Claims 1-9 and added new Claims 10-21 to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. In particular, Claims 1-9 have been amended to recite methods of screening for compounds useful for the treatment of proliferative and differentiative disorders wherein a change is detected in Skp2 binding activity or Skp2 ubiquitin ligase activity. Support for amended Claims 1-9 is found in the specification at, *e.g.*, p. 50, line 17, to p. 51, line 30; p. 93, line 32, to p. 96, line 26; and p. 97, line 16, to p. 107, line 2. New Claims 10-21 recite methods of screening for compounds useful for the treatment of proliferative and differentiative disorders wherein a change is detected in Skp2 ubiquitin ligase activity. Support for Claims 10-21 is found in the specification, in addition to the support noted above, at, *e.g.*, p. 50, line 17, to p. 51, line 30; p. 16, lines 1-19; p. 94, line 14 to p. 96, line 26; and p. 97, lines 16-26.

As such, Claims 1-21 are pending. No new matter has been added by this amendment.

1. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner rejects Claims 1-9 under 35 U.S.C. § 112, second paragraph, for being indefinite. Applicants submit that the rejections have been obviated or overcome for the reasons set forth below.

The Examiner contends that the activity of Skp2 as recited in Claims 1-9 is not defined in the specification, as Skp2 has associations with numerous proteins within the cell, as well as ubiquitin ligase activity. Although Applicants do not agree with the Examiner's contention, Claims 1-9 have been amended, simply to advance prosecution, to recite specific Skp2 activities relating to interactions with Skp2 substrate molecules. Further, Claims 10-21 have been added to recite screening methods for detecting Skp2 ubiquitin ligase activity. These claims are fully described by the specification as filed.

Applicants submit that the amendment of Claims 1-9 and the addition of Claims 10-21 overcomes the outstanding rejections.

In view of the foregoing, Applicants submit that the rejection for indefiniteness under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The Examiner has rejected Claims 1-9 as being obvious in view of Yu, *et al*, 1998, Proc. Natl. Acad. Sci. USA, 95:11324-11329 ("Yu") combined with Amati, *et al.*, 1999, Nature Cell Biol., 1:E91-E93 ("Amati"). Applicants submit that the rejection is in error for the reasons set forth below.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Further, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. 2142.

This rejection appears to be based on the Examiner's erroneous assumption that the human Cul-1 protein is the same as the Cks1 protein. Applicants submit that, as detailed below and discussed previously in the Amendment filed February 25, 2004 in connection with this application, the Cks1 required by the claimed methods is distinct from "Cul-1" referred to in the cited references.

Yu and Amati do not make obvious the claimed invention because these references fail to teach or suggest the claimed invention. The present invention relates to screening assays for compounds that alter Skp2 interaction with its substrates or Skp2-mediated ubiquitin ligase activity. The invention is based, in part, on the discovery by the inventor that Cks1 is a novel mediator of the SCF^{Skp2} ubiquitin ligase pathway. In particular, the inventor discovered that Cks1 stimulates the binding of Skp2 and p27 to mediate the ubiquitination and degradation of the substrate p27. This novel interaction between Skp2, p27, and Cks1

was used to design novel assays to screen for compounds useful for the treatment of proliferative and differentiative disorders. Pending Claims 1-21 are specifically directed to such novel screening assays and require Cks1 as an essential element of the claimed invention based on the newly discovered interaction between Cks1 and Skp2.

As discussed below, the references on which the Examiner relies for the instant rejection relate to interactions between Skp2, p27, and Cul-1, but do not recognize the existence of the novel cofactor Cks1. These references therefore do not render obvious the methods of the present invention.

Yu describes interactions between Cul-1 and the Skp1/Skp2 complex. In particular, Yu describes the Skp1/Skp2/Cul-1 complex "SCF^{Skp2}" and its possible function as an E3 ligase to selectively target cyclin D and p21 for degradation. However, Yu does not teach a complex containing Skp2 and Cks1, and does not even mention Cks1.

Amati summarizes research by others relating to interactions between Skp2 and p27. Amati does not disclose any complexes containing Cks1, nor does Amati suggest any interactions between Cks1 and Skp2.

Cul-1 and Cks1 are different proteins, as described in the specification. The specification clearly distinguishes between Cul-1 and Cks1 as proteins being vastly different in size and activity. As described in the specification, these proteins are so different they do not even belong to the same family of proteins. As set out in the specification, human Cks1 is a 10 kDa protein and member of the Suc1/Cks (cyclin dependent kinase subunit) family of proteins (see p. 3, lines 22-27). Cks1 binds Skp2 and phosphorylated p27 and is the factor required for ubiquitin ligation to p27 (see p. 97, lines 26-27, p. 105, line 27 to p. 106, line 9, and Figure 46).

On the other hand, Cul-1 is an approximately 100 kDa protein and a member of the family of cullin proteins (see the specification at p. 3, lines 10-11, and p. 77, lines 17-19). Cul-1 is a part of the SCF^{Skp2} complex, along with Skp1, Skp2, and ROC/Rbx1 (see p. 3, lines 15-17, and p. 77. lines 17-24). Thus, Cul-1 is a significantly larger protein than the 10 kDa Cks1, and has activity completely distinct from Cks1. The data presented in Figure 45C distinguishes Cul-1 from Cks1 in terms of activity, as it indicates that the SCF^{Skp2} complex containing Cul-1 still requires the factor from Fraction 1 (later identified as Cks1) for p27-ubiquitin ligation (p. 18, lines 5-6; p. 102, lines 7-32). As such, Cul-1 and Cks1 are clearly

distinct, and Applicants have therefore met their burden in proving that the novel interaction between Skp2 and Cks1, and/or Skp2, Cks1, and p27, is different from the prior art.

Thus, the references of Yu and Amati do not teach or make obvious the methods of the invention. Neither Yu or Amati mention or suggest Cks1 or its interaction with Skp2 or p27. Yu combined with Amati fails to suggest assays comprising contacting a test compound with a cell or a cell extract expressing Cks1 and Skp2 or Cks1, p27 and Skp2, and detecting a change in the interaction of Skp2 with a Skp2 substrate, or detecting a change in Skp2 ubiquitin ligase activity. Therefore, the methods of the claimed invention are not made obvious in view of the prior art cited by the Examiner. In view of the foregoing, Applicants submit that the rejection for obviousness under 35 U.S.C. §103(a) is in error and should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims is requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Respectfully submitted,

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